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Carbon Monoxide and Cardiovascular Disease: An Analysis of the Weight of Evidence

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The role, if any, of environmental tobacco smoke (ETS) in the causation and/or exacerbation of cardiovascular disease remains to be proven and defined. Earlier workers suggested that ETS-associated carbon monoxide, nicotine, and/or polyaromatic hydrocarbons may be causative factors. The purpose of this review was to assess the weight of evidence supporting a role for ambient carbon monoxide in the etiology of human ischemic cardiovascular disease. The findings show that there is scant clinical or experimental evidence to support a role for carbon monoxide in the causation of ischemic heart disease. Further, the results of field studies of relative air quality in nonsmoking and smoking homes, offices, and public places show that ETS contributes only minor and toxicologically insignificant increments in ambient carbon monoxide concentrations. These increments are variable and easily masked by other common carbon monoxide sources such as internal combustion engines and the burning of cooking and heating fuels. It is concluded that if ETS plays a role in the etiology of cardiovascular disease, it is most likely not mediated through carbon monoxide. © 1993 Academic Press, Inc.

INTRODUCTION

Cigarette smoking is frequently implicated as a risk factor in the production and/or exacerbation of cardiovascular disease. Active smoking has been estimated to impart a risk for heart disease of 1.7 relative to nonsmoking (Surgeon General, 1983).

Since 1984 a number of epidemiological studies have been conducted to assess the presence or absence of an association between the cohabitation of nonsmokers with smokers and death from cardiovascular disease. Glantz and Parmley (1991) reviewed the results of 13 such studies and pointed out that in most (9/13, 69%) the estimated relative risk (RR) of cardiovascular death due to ETS exposure was not significantly different from that of non-ETS-exposed people. In the remaining 4 studies (31% of the studies reviewed) small elevations in RR, ranging from 1.2 to 2.0, were considered statistically significant.

Glantz and Parmley noted that although estimates of cardiovascular death risks were only inconsistently elevated in ETS-exposed subjects, risk was not randomly distributed around unity. The computed RRs and 95% confidence intervals (CI) appear to be skewed toward elevation. Further, when the results from all studies were pooled,

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analysis revealed a statistically significant 30% increase in risk (RR = 1.3; 95% CI = 1.2 to 1.4).

Reviewers of the ETS–cardiovascular death risk issue (Glantz and Parmley, 1991; NIOSH, 1991; Taylor *et al.*, 1992; and Steenland, 1992) all noted that the known cardiotoxic compounds identified in mainstream smoke are also present in ETS. This has been considered supportive evidence for the thesis of a cause-and-effect relationship between ETS and cardiovascular disease risk. But in reaching their conclusions it is obvious that those authors gave little or no thought to one of the most basic principles of toxicology—the concept of dose–response relationships.

It is a basic tenet of both clinical and experimental toxicology that there is generally a direct relationship between the amount of chemical to which an organism is exposed and the magnitude of the physiological changes produced. This principle of dose–response relationships forms the basis through which the medical profession, industrial hygienists, and federal regulators establish nontoxic doses of drugs, acceptable daily exposure levels to food additives, and no effect levels of chemicals in the environment. Disregarding the principle of dose–response relationships would necessarily obligate prohibition of human exposure to virtually all chemicals, whether synthetic or natural.

Because of the relationship between dose and effect, the detection of a substance in the environment is only the initial step in establishing the presence of a possible human health hazard. When appraising the human health implications of exposure to any environmental factor a thorough assessment of the biological and chemical plausibilities of the purported effect is imperative. Such an assessment should address three key factors: (1) Is there a plausible toxicologic mechanism through which the material could produce the suspected effect? (2) Is the mechanism operative in the human subjects of interest? (3) Are the human subjects exposed to a sufficient quantity of the environmental factor to produce the claimed toxicological consequence?

The mechanism(s) though which either active or passive smoking might increase risk of cardiovascular disease have yet to be unequivocally defined. A prominent and frequently mentioned cause or contributor is the production of myocardial ischemia through exposure to ETS-associated carbon monoxide (Glantz and Parmley, 1991; NIOSH, 1991; Taylor *et al.*, 1992; and Steenland, 1992). The purpose of this review is to weigh the evidence relative to the hypothesis that ETS-related exposures to carbon monoxide (CO) can contribute to either the initiation or exacerbation of ischemic cardiovascular disease in humans. The results of this review show that there is little clinical or experimental evidence that is relevant to the issue and that that which is available does not support a role for ETS-associated carbon monoxide in the causation or exacerbation of ischemic heart disease in non/never-smoking humans.

MECHANISM OF ACTION OF CARBON MONOXIDE

Carbon monoxide, produced during the incomplete combustion of all organic materials, is the most extensively studied and best understood component of either mainstream or sidestream cigarette smoke. This gas avidly competes with oxygen for binding to hemoglobin (Hb). The combination of CO with HB results in the formation of carboxyhemoglobin (COHB) and compromises the transport of oxygen to the tissues of the body.

All consequences of exposure to CO are directly attributable to the production of tissue anoxia. The magnitude of anoxia, and therefore the severity of physical symp-

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toms, is related to the percentage of hemoglobin that is converted to COHb. The production of COHb is proportional to the amount of CO present in the inspired air.

The remarkable affinity of hemoglobin for the CO molecule makes the gas deceptively toxic. If the affinity of hemoglobin for oxygen is assigned a value of 1.0, its affinity for CO is greater than 200. In the clinical situation, a few minutes of inhaling air containing as little as 0.1% CO (i.e., 1000 parts per million) results in 50% of the available hemoglobin being converted to COHb. The presence of a 50% saturation of COHb is physically incapacitating and may even be lethal to the human (Smith, 1986). Toxicological consequences such as headache, dyspnea, and visual disturbances are associated with lower blood concentrations of COHb and the American Conference of Governmental and Industrial Hygienists has indicated its intent to establish 3.5% COHb as its best estimate of a no effect concentration among industrial workers chronically exposed to CO (ACGIH, 1991).

Because of the critical importance of continuous and adequate oxygenation of heart muscle, it is obvious that a cardiotoxic effect of CO is plausible. Myocardial damage caused CO-induced ischemia would be no less significant than ischemic damage secondary to coronary thrombosis or atherosclerosis. Since tobacco smoking may increase the concentration of CO in certain environments it is reasonable to assess the sensitivity of humans to CO-induced cardiotoxicity and determine the quantitative impact of indoor smoking on the CO concentration in air.

CARDIOVASCULAR EFFECTS OF CARBON MONOXIDE IN HUMANS

Stern *et al.* (1988) presented evidence of a possible CO-induced risk of cardiovascular disease in humans exposed to automobile exhaust. These workers reported a 35% excess in ischemic heart disease deaths among male traffic officers employed in tunnels in New York City. Additional evidence of probable occupational association of the deaths was the fact that elevated risk promptly declined upon cessation of the occupational exposure.

These officers were occupationally exposed to environments containing about 50 ppm of CO. Although direct measures of COHb were not reported, it has been estimated that 8 hr of exposure to 50 ppm of CO will produce a COHb concentration of 6.27% (Singh *et al.*, 1991). This indicates that the traffic officers may have had blood concentrations of COHb approximately twofold greater than the ACGIH no effect concentration.

Several investigators have studied the effects of controlled tobacco smoke or CO inhalation on exercise tolerance and cardiac rhythms. Elevated serum carboxyhemoglobin levels have been associated with decreased exercise tolerance in healthy subjects (McMurray *et al.*, 1985) and decreased exercise tolerance and increased susceptibility to exercise-induced cardiac arrhythmias in patients with coronary artery disease (Allred *et al.*, 1989; Sheps *et al.*, 1990a,b). Other workers, however, have reported the absence of effects of exposure to low concentrations of CO in patients with known coronary artery disease (Hinderliter *et al.*, 1989).

Effects in healthy human. McMurray *et al.* (1985) exposed healthy smokers and nonsmokers to cigarette smoke during strenuous exercise. These workers reported that the exposure decreased the amount of exercise required to produce exhaustion in both groups. In addition, exercise-associated changes in biochemical measurements indicated that exposure to smoke caused an increased reliance on anaerobic metabolism, evidence

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of decreased tissue oxygenation. The authors attributed these changes to systemic anoxia secondary to the formation of COHb.

McMurray *et al.* stated a belief that the exposure of their subjects was similar to a typical exposure of humans to environmental tobacco smoke. They did not, however, present quantitative information to support this contention and it is possible that their subjects were exposed to unrealistically high levels of smoke.

During the exercise portions of the experiment cigarettes were mechanically smoked, at a rate of one every 3 min, and the smoke was mixed with air and delivered directly to exercising subjects via a mouthpiece and an inhalation tube. The minimum duration of exercise was 20 min. Consequently, subjects were exposed to the smoke from approximately seven cigarettes during their exercise session. Preexercise COHb concentration in nonsmoking subjects was 1.1% and at the conclusion of the experimental session it had risen to 2.2%. Similar data for subjects who were smokers was not presented.

While the smoke exposure regimen in the McMurray *et al.* study may have caused the slight decrement in exercise performance, the relevance of the data to the exposure of humans to ETS is difficult to assess because the authors failed to report either the smoke:air ratios in the mixtures delivered to their subjects or the CO concentrations to which they were exposed. Since subjects were exposed to some portion of the smoke from approximately seven cigarettes it is possible that unrealistically high ETS and CO concentrations were used.

Levesque *et al.* (1991) studied the relationship between CO in ambient air and the formation of COHb in hockey players under game conditions. These workers found that for every 10 ppm of CO in environmental air, COHb saturation increases by 0.76%. If a similar relationship holds for McMurray's exercising subjects it is estimated that the nonsmoker's experimental exposure was to 15 ppm of CO in excess of their normal background concentrations.

Effects in humans with coronary artery disease. Studies in which coronary-artery-diseased subjects were exposed to CO prior to exercise have yielded a variety of results. These variable results are doubtless due to differences in experimental designs and measured endpoints and subject selections.

Kleinman *et al.* (1989) reported that exposure of male subjects with stable angina to 100 ppm of CO for 1 hr increased COHb saturation from a preexposure 1.5% to 2.9%. The 2.9% COHb concentration caused a more rapid onset of exercise-induced anginal pain than was experienced during the control exercise period without CO exposure.

Hinderliter *et al.* (1989) exposed coronary-artery-diseased patients, with low baseline levels of ventricular arrhythmias, to either 100 or 200 ppm of CO for sufficient durations to increase COHb levels to as high as 5.8%. Subjects then performed symptom-limited exercise. Continuous ambulatory EKG monitoring revealed that this level of COHb saturation was nonarrhythmogenic in these cardiac-diseased patients. Unfortunately, these workers did not compare pre- and postexposure susceptibility to anginal pain.

Using the same protocol with coronary-artery-diseased patients who had ventricular arrhythmias Sheps *et al.* (1990a,b) found that 5.7% COHb saturation caused an increased frequency and complexity of postexercise ventricular arrhythmias. Carboxyhemoglobin saturation of 3.9%, however, was without effect.

Allred *et al.* (1989) reported the results of a multicenter study of the effects of CO exposure on exercise performance in coronary artery disease patients. Subjects were

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exposed to either 117 or 253 ppm of CO for periods sufficient to elevate COHb concentrations to values of 2.0 or 3.9%. Under the conditions of these experiments control COHb concentrations were unusually low (0.6–0.7%). These workers reported that both the 2.0 and the 3.9% COHb concentrations exacerbated exercise-induced myocardial ischemia as evidenced by EKG changes and decreased time of onset of anginal pain.

The Allred study has been criticized (Katzenstein, 1990) because of the low control values reported for pretest blood COHb concentrations. Levels of COHb in nonexposed nonsmokers are generally found to be from two to three times higher than those reported by the Allred group. For example, Hinderliter *et al.* (1989) reported a preexposure level of 1.8%; Sheps *et al.* (1990a) reported 1.82%; and McMurray *et al.* (1985) reported 1.1%.

The Allred group explained that their low levels were due to their use of a gas chromatography assay of COHb rather than the more frequently used optically based assay (Dahms *et al.*, 1990). They stated that the commercial instruments generally provide inaccurately high COHb readings when concentrations of less than 5% are assayed. For this reason the relevance of the Allred data to other contemporary studies is open to question.

Overall, the results of studies in humans afford some evidence that exposure to extremely high concentrations of CO may elevate risk of ischemic heart disease and decrease the exercise tolerance of people with coronary artery disease. Such effects are consistent with the production of systemic anoxia and impaired myocardial oxygenation. However, it remains to be established whether ETS can contribute sufficient environmental CO to impact on the cardiovascular status of either healthy or compromised humans.

THE CLINICAL SIGNIFICANCE OF ETS-ASSOCIATED CARBON MONOXIDE

To assess the potential cardiac risk of exposure to ETS-associated CO, it is necessary to estimate a maximal COHb saturation that would produce no physiological changes in exposed humans. Concentrations of CO in excess of that value should be considered potentially dangerous to human health.

A COHb concentration of 2.5% is proposed as the no effect level. This level of saturation is far below that which was associated with increased ischemic heart disease risk in traffic tunnel workers (estimated to be 6.27% COHb) (Stern *et al.*, 1988). It is also well below the 3.9% level, a level that did not result in exercise-induced arrhythmias in patients with preexisting coronary artery disease (Sheps *et al.*, 1990a,b) and it is less than the 2.9% level that was associated with decreased exercise tolerance in coronary-artery-diseased patients (Kleinman *et al.*, 1989).

The proposed value is also lower than the 3.5% COHb saturation that the ACGIH intends to establish as its best estimate of a no effect concentration among industrial workers (ACGIH, 1991). The ACGIH value represents that body of health scientists' best estimate of a chronic, no effect level in workers exposed to CO 8 hr per day, 40 hr per week.

The 2.2% COHb concentration reported by McMurray *et al.* (1985) to produce an 8% decrement in the performance of strenuous exercise was not considered because

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the effect, which was minimal, was noted in only a small number of strenuously exercising subjects. Similarly, the 2.0% COHb saturation reported to reduce exercise tolerance in patients with coronary artery disease (Allred *et al.*, 1989) was not incorporated into the estimation of a no effect level because of uncertainty about the comparability of the COHb analyses in that study with those of the more numerous contemporary studies. In view of the available data relative to potential cardiovascular effects of CO exposure in humans, the 2.5% COHb concentration represents a conservative estimate of a probable no effect level.

The likelihood of a human achieving a serum concentration of 2.5% COHb depends upon the ambient concentration of CO and the duration of exposure. Singh *et al.* (1991) reviewed experimentally achieved COHb concentrations after exposures of varying durations to different concentrations of the gas. With exposure to 100 ppm, a serum concentration of 2.5% COHb was reached after between 30 and 45 min of exposure. At an ambient concentration of 50 ppm CO, longer than 60 min was required; and two hours exposure to 45 ppm causes a COHb concentration of 2.48%.

With the exception of accidents, employment in occupations involving internal combustion engines, and intentional self inflicted exposures, humans are seldom exposed, even for brief periods, to CO concentrations in the range of 45 to 100 ppm. At lower, more probable levels of CO exposure still longer periods are required to produce the 2.5% COHb saturation. For example, exposure to 15 ppm of CO requires continuous exposure for 10 hr to produce a serum concentration of 2.5% COHb (Guerin *et al.*, 1992).

IMPACT OF ETS ON AMBIENT CARBON MONOXIDE CONCENTRATIONS

It has been frequently and correctly noted that sidestream tobacco smoke contains a higher concentration of CO than does mainstream smoke. Sidestream smoke is produced at a lower temperature at which the combustion of carbonaceous materials is less complete. American cigarettes are recognized to deliver approximately 15 mg/cigarette of CO via mainstream smoke and 50 mg/cigarette via sidestream smoke (Guerin *et al.*, 1992).

This relatively high concentration in sidestream smoke has led many to conclude that ETS is a major contributor to environmental CO concentrations. Such a conclusion is not supported by the results generated in field studies during which the air in residences, work places, and public places has been analyzed under both smoking and nonsmoking conditions.

Guerin *et al.* (1992) reviewed the data generated during field studies of CO concentrations in a variety of smoking and nonsmoking areas. The results of the reviewed studies indicated that in general, smoking contributes only small increments in environmental CO. For example, mean concentrations of CO in the air of offices in which smoking was permitted ranged from 1.2 to 2.8 ppm, whereas values in nonsmoking areas ranged from 1.2 to 2.5 ppm. In restaurants and cafeterias permitting smoking, the environmental CO concentrations ranged from 1.2 to 9.9 ppm as contrasted against nonsmoking control areas where concentrations ranged from 0.5 to 7.1 ppm.

On the basis of the available data obtained from field studies, it is clear that ETS contributes CO to the environment. However, the increment of environmental CO

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attributable to tobacco smoking is exceedingly small. Further, this small increase is easily masked by normal day-to-day variations in ambient concentrations which are attributable to the presence of other CO sources such as automobiles and the combustion of heating and cooking fuels.

More importantly, however, the results of the field studies also show that whether or not tobacco smoking is permitted, CO concentrations to which humans are exposed seldom exceed the 9 ppm indoor standard that has been recommended by the American Society for Heating, Refrigerating, and Air Conditioning Engineers (ASHRAE, 1989).

Since 10 hr of exposure to 15 ppm of CO is required to produce a 2.5% level of COHb saturation in humans, and since this is a no effect level, few Americans are ever exposed, even for brief periods, to cardiotoxic concentrations of COHb. The small increment in ambient CO concentrations contributed by ETS is insignificant.

While conducting this analysis no attempt was made to directly address the issue of whether or not exposure to ETS per se causes or exacerbates cardiovascular disease. The results of this review have established, however, that if the purported impact of ETS on cardiovascular disease is real, it can be neither explained nor mediated through ETS-associated increases in ambient concentrations of carbon monoxide. There is scant evidence to support a role for carbon monoxide in the causation of ischemic heart disease. Further, the results of field studies of air quality in nonsmoking and smoking homes, offices, and public places demonstrate that ETS contributes only minor and toxicologically insignificant increments in ambient carbon monoxide concentrations. These increments are variable and easily masked by other commonly encountered carbon monoxide sources such as internal combustion engines and the burning of cooking and heating fuels.

Earlier workers have suggested that inhalation exposure to environmental tobacco smoke-associated nicotine and/or polycyclic aromatic hydrocarbons may also cause cardiovascular disease in humans (Glantz *et al.*, 1991; NIOSH, 1991; Taylor *et al.*, 1992; and Steenland, 1992). Such claims cannot be taken seriously at this time since critical reviews of the experimental and clinical evidence claimed to support the hypotheses have yet to be conducted.

CONCLUSION

If ETS is an etiological factor in cardiovascular disease, its effect is most likely not mediated through carbon monoxide.

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